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FLOOD, MICHELE C	
ART UNIT	**PAPER NUMBER**
1655	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/698,863	GHOSH ET AL.	
	Examiner	Art Unit	
	Michele Flood	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-8 and 10-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-8 and 10-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/20/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of the receipt of Applicant's remarks and request for reconsideration of the pending claims.

The Examiner thanks Dr. Mengmeng Fahrni for forwarding references cited in Applicant's "REMARKS" filed on August 18, 2006.

The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 2, 4-8 and 10-13 are under examination.

Response to Arguments

Claim Rejections - 35 USC § 102

Legal Standard for Anticipation/Inherency Under - 35 USC § 102

To anticipate a claim under 35 US.C. 102(b), a single prior art reference must place the invention in the public's possession by disclosing each and every element of the claimed invention in a manner sufficient to enable one skilled in the art to practice the invention. *Scripps Clinic & Research Foundation v. Genetech, Inc.,* 927 F.2d 1565, 1576, 18 U.S.P.Q.2d 1001, 1001 (Fed. Cir. 1991); *In re Donahue,* 766 F2d531, 533, 266 U.S.P.Q. 619, 621 (Fed. Cir. 1985). To anticipate, the prior art must either expressly or inherently disclose each limitation of the claimed invention, *MEHL/Biophile Int'l Corp. v. Milgraum,* 192F.3d 1362, 1365, 52 U.S.P.Q.2d 1303, 1303 (Fed. Cir. 1999) (citing to *In re Schreiber,* 128 F.3d 1473, 1477, 44 U.S.P.Q. 1429, 1431 (Fed. Cir. 1997)); *Atlas Powder Co. v. Ireco, Inc.,* 190 F.3d 1342, 1347, 51 U.S.P.Q.2d 1943, 1946

(Fed. Cir. 1999). To inherently anticipate, the prior art, the prior art must necessarily function in accordance with, or include, the claimed limitations. *MEHL/Biophile,* 192 F.3d at 1365, 52 U.S.P.Q.2d at 1303. However, it is not required that those of ordinary skill in the art recognize the inherent characteristics or the functions of the prior art. *Id.* Specifically, discovery of the mechanism underlying a known process does not make it patentable.

Claims 1, 2, 4-8, 10, 12 and 13 remain rejected under 35 U.S.C. 102(b) as being anticipated by Aoyama et al. (N). Applicant's arguments have been fully considered. However, the rejection stands for the reasons set forth in the previous Office action and for the reasons set forth below.

Applicant claims a method of preventing and/or treating asthma in animals including humans using natural compound luteolin, said method comprising administering a composition consisting essentially of a therapeutically effective dose of the luteolin to the animal, wherein the luteolin is administered orally, and wherein the luteolin is administered in an amount in a range or 0.1 to 10mg/kg of body weight of the animal.

Applicant's main argument is directed to the idea that Aoyama fails to anticipate the instantly claimed invention because Aoyama does not teach what amount of luteolin has an anti-asthmatic effect, when administered at the dosage rate in the instantly claimed method. Applicant further questions the pharmacological assessment of operability and efficacy, as well as the toxicity, made by Aoyama since testing of the inhibitors for anti-asthmatic activity was performed using an *in vitro* cell culture system,

and not an *in vivo* animal model system. Thus, Applicant concludes that the method taught by Aoyama is not supported by any valid experimental evidence or publication.

Each of Applicant's arguments have been fully considered but found unpersuasive because Aoyama teaches a method of preventing and/or treating asthma in animals comprising orally administering an effective amount of an alcoholic extract obtained from the *Perilla* seed, which comprises luteolin or a concentrated extract therefrom comprising luteolin alone; and, also a method of preventing and/or treating asthma in animals comprising the oral administration of a composition comprising a therapeutically effective dose of luteolin alone to an animal. While Aoyama does indicate that apigenin has the highest activity, Applicant should not look at the teachings of Aoyama in a vacuum because Aoyama clearly teaches that luteolin, as well as apigenin and other disclosed compounds, is useful and capable of effectively treating and/or preventing asthma by oral administration of therapeutic amounts thereof. For example, Aoyama teaches each of the disclosed histamine isolation inhibitor compounds, as well as the crude product extract from which they are obtained, as a histamine release inhibitor, which is extremely good in action of inhibiting the release of histamine or the development of asthmatic features comprising Early Airway Response (EAR). In [0027], Aoyama clearly teaches administering 0.5-3000 mg/day of the referenced histamine isolation inhibitor or 0.3 to 15% weight percent or 0.01-10 weight percent to a patient in need thereof of treatment. Hence, Aoyama expressly teaches each of apigenin, chrysoeriol, luteolin and rosmarinic acid as histamine release inhibitors, as well as *Perilla* seed alcohol extracts containing the aforementioned

compounds and an EtOAc fraction of *Perilla* seed extract as inhibitors of histamine release, which are useful in the prevention and/or treatment of allergic disease conditions, such as asthma. Furthermore, in [0010], Aoyama expressly teaches that luteolin can be extracted from perilla seed and used in the making of both drugs and food products to provide an oral delivery vehicle for use in the disclosed method of treatment, such as the food product comprising luteolin alone discussed at [0058].

Contrary to Applicant's argument that Aoyama does not teach treatment of asthma comprising the administration of a composition consisting essentially of luteolin, Aoyama expressly teaches that the bioactive compounds contained in the disclosed *Perilla* seed extract can be concentrated, condensed or isolated from the plant seed extract, in [0020] through [0023]. Aoyama also teaches that while the referenced extracts are considered as histamine release inhibitors, refining of the active principle compounds contained therein the extracts can be isolated and that fractions with the highest activity can be collected and used as histamine release inhibitors for treatments or prophylaxis of allergic diseases, such as asthma. In [0031], Aoyama teaches a method of isolating luteolin from *Perilla* seed extract. Hence, the method of treatment taught by Aoyama is not only directed to the administration of effective amounts of *Perilla* seed extract or fractions thereof comprising luteolin but also the administration of effective amounts of each of the individual compounds contained therein (including luteolin) to provide the claimed beneficial functional effect for the claim-designated disease condition. *See* [0010], wherein Aoyama expressly teaches that each of

apigenin, chrysoeriol, luteolin and rosmarinic acid may be efficiently extracted from the seed extract and used in the making of therapeutic preparations for oral administration. Applicant is also directed to [0006] wherein Aoyama clearly teaches that that the disclosed compositions useful for treating and/or preventing asthma may consist essentially of one or more of the disclosed histamine release inhibitors, such as luteolin. Again, the Office points to [0027] wherein Aoyama clearly teaches the effective dose range amounts of the histamine release inhibitors for the making of oral pharmaceuticals to be administered to patients in the treatment or allergic diseases, such as asthma: "0.5-3000 mg is usually suitable for in an adult, although a dose may change with the age or a medication method, condition of disease, and a patient etc. at 0.5-500 mg and a child as an active principle per day ...". Furthermore, in [0029], Aoyama expressly teaches that the referenced histamine isolation inhibitors can substantially reduce an allergic response, such as cellular degranulation (an asthmatic feature of Late Airway Response). For instance, Aoyama teaches, "Therefore, the histamine isolation inhibitor of this invention can treat or prevent effectively the pollinosis which is many symptoms of I-beam allergy, asthma, dry grass heat, rhinitis, urticaria, a drug allergy, etc. Moreover, it becomes possible to prevent allergy in an every day life and to improve a body easily with the allergy prevention external preparations and allergy prevention food containing the histamine isolation inhibitor of this invention." Moreover, Aoyama clearly teaches that the administration of the referenced compounds, including luteolin, and extracts or fractions thereof comprising luteolin inhibit the release of histamine, which is a symptomatic developmental feature of EAR;

and, as set forth immediately above, Aoyama clearly teaches that the referenced histamine isolation inhibitors substantially reduce cellular degranulation, which is a symptomatic developmental feature of LAR. In [0002] - [0003], Aoyama also clearly describes the progressive biomechanisms that lead to the development of allergic responses in allergic disease, such as asthma, and expressly teaches that by controlling or suppressing the release of histamine, one may also prevent symptoms of LAR, *e.g.,* the production of mast cells and IgE. Since, the administration of effective amounts of the compositions taught by Aoyama inhibits the release of histamine, the method of treatment taught by Aoyama would indeed prevent the development of asthmatic features comprising both EAR and LAR.

Applicant reasonably argues that there scientific literature suggests that the delivery of therapeutic drugs to an *in vivo* experimental system, such as a cell culture system, which exhibit activity against a targeted disease condition do not necessarily have the same beneficial functional effect in an *in vivo* animal model, such as the rat model used to test the efficacy of luteolin for anti-asthmatic activity. However, one may reasonably argue that while *in vitro* and *in vivo* models used for the testing of candidate agents against a disease condition may exhibit activity against a targeted disease condition that these same agents heralded as breakthrough drugs do not have the same functional effects in humans bearing the disease condition. Without a clear and convincing reason that the cell culture system used to test the efficacy of luteolin as an anti-asthmatic agent is not sufficient as a working example or an enabling feature of the method taught by Aoyama comprising the administration of luteolin, including oral

administration to treat and prevent asthma, and given that Applicant has not shown that the method of treatment taught by Aoyama would not inherently encompass the claimed functional effects for the prevention of the development of asthmatic features comprising Early Airway Response (EAR) and Late Airway Response, and the claimed functional effects of increasing IFN-gamma to a normal level and decreasing each of IL-5, IL-4 or IgE to a normal level and the inhibition of airway constriction and airway hyperactivity are not inherent to the method of treatment and/or prevention taught by Aoyama, absent sufficient and convincing evidence to the contrary, the instantly claimed method and functional effects thereof are deemed inherent to the teachings of Aoyama.

Finally, while Applicant may continue to argue that Aoyama does not expressly teach that the referenced method of treatment prevents development of asthmatic features comprising Early Airway Response (EAR) and Late Airway Response, or any of the claimed functional effects of increasing IFN-gamma to a normal level and decreasing each of IL-5, IL-4 or IgE to a normal level, or wherein luteolin inhibits airway constriction or airway hyperactivity, *per se*; however, the method of treatment taught by Aoyama comprises the oral administration of the same ingredient in the same amounts to provide the same beneficial functional effect for the prevention of asthma in patients in need thereof of such treatment. Therefore, the claimed functional effects for the prevention of the development of asthmatic features comprising Early Airway Response (EAR) and Late Airway Response, and the claimed functional effects of increasing IFN-gamma to a normal level and decreasing each of IL-5, IL-4 or IgE to a normal level and

the inhibition of airway constriction and airway hyperactivity are inherent to the method of treatment taught by Aoyama.

Based on the foregoing, the Office believes that the anticipatory rejection based on inherency is proper given that Applicant has not provided a clear and convincing argument that the instantly claimed product-by-process is an act of invention rather than mere observation.

The reference anticipates the claimed subject matter.

Claims 1, 2, 4-8 and 10-13 remain rejected under 35 U.S.C. 102(b) as being anticipated by Wang (U). Applicant's arguments have been fully considered. However, the rejection stands for the reasons set forth in the previous Office action and for the reasons set forth below.

Applicant argues that the teachings of Wang are directed to the use of luteolin for the treatment of patients with bronchitis, and not patients with asthma. Applicant further argues that Wang does not disclose evaluating luteolin on a single characteristic feature or biochemical parameter of asthma. Thus, Applicant concludes that Wang fails to anticipate the instantly claimed invention and asserts that the Examiner's rejection based on inherency is flawed: "Therefore, the assertion that the functional effects for preventing the development of asthmatic features of LAR AND EAR, and of increasing IFN-α to a normal level and decreasing each of IL-4, IL-5, and IGE to a normal level, as well as inhibiting airway constriction and airway hyperactivity are inherent to the method of treatment taught by Wang is an extrapolation at best." *See* page 7, paragraphs 3-5

of Applicant's "REMARKS" filed on August 18, 2006. However, Applicant's arguments are unpersuasive the record for prosecution of the present application shows that Applicant has already provided a nexus between the disease conditions of bronchitis and asthma: Mainly, there exists a population of patients suffering from asthma associated with bronchitis and a population of patients suffering bronchitis who are susceptible to the development of asthma since it is well known in the art of medicine that asthma is a symptom of bronchitis, as clearly indicated by the teachings of Wang and as readily admitted by Applicant in the "Remarks" filed on July 26, 2005. Moreover, Wang teaches a method of orally administering an effective amount of luteolin obtained from plant sources (120 mg/day p.o.) for 10 days to patients with bronchitis. On page 148, Column 2, under "*Clinical Studies*", Wang teaches, "The major symptoms of chronic bronchitis, including cough, asthma, sputum and wheezing, were effectively alleviated with luteolin treatment (Table VI). No liver, cardiac or renal toxicity was reported." Thus, while Applicant may argue that Wang's method of treating patients with asthma associated with bronchitis comprising the administration of effective dose amounts of a composition consisting essentially of luteolin does not necessarily lead one to the conclusion that all asthma patients including those not suffering from bronchitis would be effectively treated by luteolin, the Office notes that Wang clearly teaches the instantly claimed invention because Wang teaches a method of treating asthma comprising the oral administration of therapeutically effective amounts of luteolin (in the same amounts as instantly claimed by Applicant) to a patient population suffering asthma with associated bronchitis, wherein the referenced method was taught

as effectively alleviating symptoms of asthma; and, thereby, Wang also teaches the instantly claimed method for the prevention of asthma because Wang teaches that the oral administration of therapeutically effective amounts of luteolin (which are the same amounts as instantly claimed by Applicant) to patient population susceptible to the development of asthma, effectively eliminates symptoms of asthma. See Table IV, on page 148, wherein Wang indicates a rate of 93.3% complete remission of asthma symptoms in bronchitis patients treated with luteolin.

Contrary to Applicant's argument, the Examiner does not misapply the doctrine of inherency based on extrapolation for determining anticipation of the instantly claimed invention in view of the teachings of Wang. Clearly, the Examiner provided sufficient basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristics necessarily flows from the teachings of the applied prior art. Applicant is invited to revisit the previous Office action wherein on pages 7-10, the Examiner set forth the terms and the reasoning for rejecting the instantly claimed subject matter based on inherency with regard to the anticipatory teachings of Wang (and set forth below for convenience):

Thus, while Wang does not expressly teach that the referenced method of treatment prevents development of asthmatic features comprising Early Airway Response (EAR) and Late Airway Response, or any of the claimed functional effects of increasing IFN-gamma to a normal level and decreasing each of IL-5, IL-4 or IgE to a normal level, or wherein luteolin inhibits airway constriction or airway hyperactivity, *per se*, the method of treatment taught by Wang comprises the oral administration of the

same ingredient in the same amounts to provide the same beneficial functional effect for at least the treatment of asthma in patients suffering bronchitis in need thereof of such treatment and at least the prevention of asthma in patients in need thereof of such treatment. Therefore, the claimed functional effects for the prevention of the development of asthmatic features comprising Early Airway Response (EAR) and Late Airway Response, and the claimed functional effects of increasing IFN-gamma to a normal level and decreasing each of IL-5, IL-4 or IgE to a normal level and the inhibition of airway constriction and airway hyperactivity are inherent to the methods of treatment and/or prevention taught by Wang, especially in view of Wang teaching that luteolin treatment provided a rate of 93.3% complete remission of asthma symptoms in bronchitis patients treated with luteolin.

On page 15 of Applicant's "REMARKS", first paragraph, Applicant asserts that the novelty of the presently claimed invention is found in Applicant's disclosure for the anti-asthmatic effects of luteolin to modulate certain biochemical and biophysiolgical mechanisms associated with the development of symptoms of asthma comprising the administration of low doses of the drug to an *in vivo* animal model of asthma. However, Applicants' arguments are not persuasive because of the foregoing case law:

> "There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003) (rejecting the contention that inherent anticipation requires recognition by a person of ordinary skill in the art before the critical date and allowing expert testimony with respect to post-critical date clinical trials to show inherency); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004)("[T]he fact that a characteristic is a necessary feature or result of a prior-art

> embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention."); *Abbott Labs v. Geneva Pharms., Inc.*, 182 F.3d 1315, 1319, 51 USPQ2d 1307, 1310 (Fed.Cir.1999) ("If a product that is offered for sale inherently possesses each of the limitations of the claims, then the invention is on sale, whether or not the parties to the transaction recognize that the product possesses the claimed characteristics."); *Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1348-49 (Fed. Cir. 1999) ("Because 'sufficient aeration' was inherent in the prior art, it is irrelevant that the prior art did not recognize the key aspect of [the] invention.... An inherent structure, composition, or function is not necessarily known.")>; *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343-44, 74 USPQ2d 1398, 1406-07 (Fed. Cir. 2005) (holding that a prior art patent to an anhydrous form of a compound "inherently" anticipated the claimed hemihydrate form of the compound because practicing the process in the prior art to manufacture the anhydrous compound "inherently results in at least trace amounts of" the claimed hemihydrate even if the prior art did not discuss or recognize the hemihydrate)<."

Given that Wang clearly teaches administering the same ingredient and the same ingredient in the same amounts to a patient population suffering from asthma, as disclosed by Applicant, has the functional effect to alleviate asthmatic conditions and remission of the disease thereof without toxic side effects; and given that Applicant has not shown that the method of treatment taught by Wang would not inherently encompass the claimed functional effects for the prevention of the development of asthmatic features comprising Early Airway Response (EAR) and Late Airway Response, and the claimed functional effects of increasing IFN-gamma to a normal level and decreasing each of IL-5, IL-4 or IgE to a normal level and the inhibition of airway constriction and airway hyperactivity are not inherent to the method of treatment and/or prevention taught by Wang, absent sufficient and convincing evidence to the contrary, the instantly claimed method and functional effects thereof are deemed inherent to the teachings of Wang. Clearly, a teaching for the alleviation of asthma

symptoms in patients with bronchitis associated with asthma and the remission of asthma comprising the administration of dose dependent amounts of luteolin, such as fully taught by Wang, defines a clear teaching for the anti-asthmatic activity of luteolin.

Based on the foregoing, the Office believes that the anticipatory rejection based on inherency is proper given that Applicant has not provided a clear and convincing argument that the instantly claimed method is an act of invention rather than mere observation.

The rejection anticipates the claimed subject matter.

Claims 1, 2, 4-8 and 10-13 remain rejected under 35 U.S.C. 102(b) as being anticipated by Murai et al. (A*). Applicant's arguments have been fully considered. However, the rejection stands for the reasons set forth in the previous Office action and for the reasons set forth below.

Applicant's argument is directed to the idea that Murai does not anticipate the instantly claimed subject matter because the patent reference does not teach treating asthma comprising administering luteolin to an animal model. Applicant has misread the Examiner's rejection because the claims were rejected as being anticipated by Murai for preventing asthma, and not necessarily treating asthma. Therefore, Applicant's arguments are not persuasive because Murai teaches a method of preventing asthma in animals comprising the oral administration of a therapeutically effective amount of luteolin, wherein the luteolin is administered in an amount range of 0.5 to 5000 mg to adults and in an amount range of 0.5 to 3000 mg to children for a

least a time period in a range of 5 to 10 days. *See* Column 1, line 16 to Column 2, line 52; Column 5, lines 11-15; Column 10, lines 47-67; and, patent Claims 8, 12, 16, 17 and 18.

Applicant also argues that Murai fails to anticipate the instantly claimed invention because "not all anti-alllergic agents are anti-asthmatic agents; and, it would not have been clear that luteolin had anti-asthmatic properties without *in vivo* testing". Applicant asserts that the Examiner has misapplied the principles of inherency and argues that Murai neither teaches nor suggests the treatment of asthma comprising the administration of luteolin. This is not true. For example, in Column 1, lines 16-38, Murai expressly teaches that inhibitors of lipoxygenase, such as luteolin, are useful in the inhibition of activities of 5-lipoxygenase and 12-lipoxygenase in relation to the metabolism of arachidonic acid, which induces the formation of leukotrienes associated with allergic disease, inflammatory responses and asthma. Murai also teaches that inhibitors of lipoxygenase may be used to combat and/or regulate allergic diseases, in Column 2, lines 16-25.

Applicant further argues that without *in vivo* testing it would not have been clear that luteolin had anti-asthmatic properties. However, Applicant's argument is not persuasive because by way of demonstration Murai teaches the anti-asthmatic effects and anti-inflammatory effects of luteolin using a control test against oxazolone-induced inflammation in the ears of mice (known in the art as an animal model for asthma) Column 10, line 65 to Column 11, line 11. Also *see* Table 3, wherein Murai compares the anti-inflammatory response of luteolin to other anti-asthmatic drugs. In Column 8, in

its entirety, Murai also teaches the strong inhibitory activity of luteolin against 5-LO. Since each of the cell culture system and animal model used in the testing of luteolin are well accepted and well-established models for testing the efficacy of drugs for the treatment of asthma, the *in vitro* and *in vivo* model assays reasonably correlate to working examples of the patent method. Moreover, even Applicant readily admits, "Only certain anti-inflammatory compounds, such as steroids and anti-leukotrienes have been shown to have efficacy in treating asthma (Gupta et al., 2004), on page 2 of Applicant's "REMARKS".

Thus, while Murai does not expressly that teach the referenced method prevents development of asthmatic features comprising Early Airway Response (EAR) and Late Airway Response, or any of the claimed functional effects of increasing IFN-gamma to a normal level and decreasing each of IL-5, IL-4 or IgE to a normal level, or wherein luteolin inhibits airway constriction or airway hyperactivity, *per se*, the method of prevention taught by Murai comprises the oral administration of the same ingredient in the same amounts to provide the same beneficial functional effect for at least the prevention of asthma. Therefore, the claimed functional effects for the prevention of the development of asthmatic features comprising Early Airway Response (EAR) and Late Airway Response, and the claimed functional effects of increasing IFN-gamma to a normal level and decreasing each of IL-5, IL-4 or IgE to a normal level and the inhibition of airway constriction and airway hyperactivity are inherent to the method for the prevention of asthma taught by Murai.

The reference anticipates the claimed subject matter.

Claim Rejections - 35 USC § 103

Claims 1, 2, 4-8 and 10-13 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Murai et al. (A*) in view of Tanaka et al. (U) and Nagai et al. (W). The rejection stands for the reasons set forth in the previous office action and set forth below.

Firstly, the Examiner recognizes asthma as a complex chronic inflammatory disease of the airways that involves the activation of multiple inflammatory mediators and cell structures by several different biochemical pathways to exert many pathophysiological changes in asthmatic patients. Thereby, in no way does the Examiner view Applicant's disclosure as being very simple and obvious using impermissible hindsight. However, while Applicant may have elucidated the anti-asthmatic properties of luteolin by identifying the biochemical and biophysical mechanisms to exert the functional effect to treat and/or prevent asthmatic features in a patient, given the prior art at the time the invention taught the anti-asthmatic activities of luteolin, Applicant's claimed invention is anticipated by the prior art; and/or at least would have been at least *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially given the anticipatory teaches of Aoyama, Wang, and Aoyama, which disclose the anti-histamine, anti-inflammatory, anti-asthmatic and activity against lipoxygenase inhibitors for the administration of luteolin to either treat or prevent or treat and/prevent asthma by inhibiting key biochemical pathways, the

production of inflammatory mediators and cellular structures, and physical changes responsible for the induction of characterized asthmatic features.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the primary reference of Murai was relied upon for the reasons set forth in the previous Office action and for all of the reasons set forth herein. Because Murai did not expressly teach a method of treating asthma in animals comprising the administration of a therapeutically effective dose amount of luteolin to animals *per se*, the secondary teachings of Tanaka and Nagai were relied upon because Tanaka suggested the use of luteolin as an anti-

allergic drug for the treatment of asthma in patients because flavonoids, such as luteolin, inhibit activity of hexosaminidase release from mast cells, inhibit the release of histamine from mast cells or basophils and suppress cysteinyl leukotriene synthesis through an inhibition of phospholipase A2 (PLA2) and/ or 5-lipoxygenase, on page 59, second paragraph to page 60, first paragraph; and, like Tanaka, Nagai suggested the use of luteolin for the treatment of asthma. Thus, at the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to adapt the method of preventing asthma taught by Murai to the instantly claimed method of treating asthma in a patient because Murai taught luteolin as an inhibitor of 5-lipoxyoxygenase, which metabolizes arachidonic acid into 5-hydroxy-6,8,10,14-eicosatetraenoic acid (5-HETE), and induces the formation of leukotriene (LT) which is associated with allergic diseases, inflammatory disease and asthma, in Column 1, lines 33-43; and, Tanaka taught, "The inhibitory effect of several flavonoids (such as the luteolin used in the method of treatment taught by Murai) on the PLA2 and 5LO was recently reviewed [citation omitted]. PLA2 releases arachidonic acid from membrane phospholipids and is metabolized by the 5LO pathway, leading to biosynthesis of cysteinyl leukotrienes, which are important mediators for pathogenesis of asthma", on page 60, lines 6-11; moreover, on page 60, second Column, first paragraph, Tanaka teaches that luteolin inhibited the production of both IL-4 and IL-5; and, Nagai demonstrated the effect of luteolin to inhibit both histamine release from mast cells and cytokine production, the inhibition of immediate phase reaction and late

phase reaction in relation to allergic reactions with IgE-dependent mast cells, which are mediators of asthma pathogenesis.

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

No claims are allowed.

* Applicant is advised that the cited U.S. patents and patent application publications are available for download via the Office's PAIR. As an alternate source, all U.S. patents and patent application publications are available on the USPTO web site (www.uspto.gov), from the Office of Public Records and from commercial sources. Should you receive inquiries about the use of the Office's PAIR system, applicants may be referred to the Electronic Business Center (EBC) at http://www.uspto.gov/ebc/index.html or 1-866-217-9197.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele Flood whose telephone number is 571-272-0964. The examiner can normally be reached on 7:00 am - 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on 571-272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michele C. Flood

MICHELE FLOOD
PRIMARY EXAMINER

Michele Flood
Primary Examiner
Art Unit 1655

MCF
October 28, 2006